Remarks

Claims 8-10 were pending in the subject application. By this Amendment, applicant has amended claim 8. Accordingly, claim 8-10 are pending in the subject application.

In section 3 of the December 20, 2004 Final Office Action, the Examiner objected to claim 8 because the "™" after Sepharose has been deleted.

In response and pursuant to MPEP §§ 608.01(v), 706.03(d) and 2173.05(u), applicant has amended claim 8 to recite "a N-hydroxysuccinimide (NHS-)-activated highly cross linked 4% agarose column". Applicant has also amended page 18 of the specification to recite "N-hydroxysuccinimide (NHS)-activated Sepharose™ High Performance Column (Pharmacia 17-0717-01, highly cross linked 4% agarose)". Support for these amendments may be found in the product specification of N-hydroxysuccinimide (NHS)-activated Sepharose™ High Performance Column, Product No. 17-0717-01, a copy of which is attached hereto as **Exhibit A.**

Rejections under 35 U.S.C. §103(a)

In section 6 of the December 20, 2004 Final Office Action, the Examiner rejected claims 8-10 under 35 U.S.C. §103(a) as allegedly unpatentable over Gaubitz, M., et al., Journal of Autoimmunity, (1999), 11:495-501 ("Gaubitz") in view of U.S. Patent No. 6,228,363, issued May 8, 2001 (Naparstek) with a priority date of March 20, 1998 ("the '363 patent") and Madaio, M., et al., Journal

of the American Society of Nephrology, (1996), 7:387-396 ("Madaio").

As in the previous office action, the Examiner again alleged that Gaubitz teaches a method of treating lupus comprising extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies. The Examiner also alleged that Gaubitz further teaches that dsDNA-Ab play a "pivotal" role in the pathogenesis of SLE and that their removal proved useful for the treatment of the disease citing the Introduction and the Discussion sections. The Examiner acknowledged that Gaubitz's teaching differs from the claimed invention in that it does not teach a method employing a column comprising the R38 peptide nor the use of a Sepharose™ column. The Examiner alleged that the '363 patent teaches that the R38 peptide is derived from laminin and is recognized by pathogenic lupus antibodies citing column 3, lines 13-19. The Examiner also alleged that Madaio teaches that dsDNA-Ab from lupus patients also recognize laminin citing the Abstract.

The Examiner concluded it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method of treating lupus comprising extracorporeal column immunoadsorption of a subject's plasma for the removal of pathogenic antibodies, as taught by Gaubitz, employing the R38 peptide of the '363 patent. One of ordinary skill in the art at the time the invention was made would have been motivated to employ the R38 peptide on an immunoadsorption column given the teaching of Madaio that dsDNA-Ab from lupus patients also recognize laminin and the teaching of the '363 patent that

the R38 peptide is derived from laminin and is recognized by pathogenic lupus antibodies. The Examiner included claim 8 in the rejection because various types of immunoadsorber matrices (including Sepharose™) for column chromatography were well-known in the art at the time of the invention. The Examiner alleged that the choice of any particular immunoadsorber matrix would have comprised only routine optimization of the claimed method and would have been well within the purview of one of ordinary skill in the art at the time of the invention. The Examiner alleged that new claim 10 does not recite any new limitations because all ligands are coupled to Sepharose™ in some sort of "coupling buffer". The Examiner further alleged that an ordinarily skilled artisan would know that Sepharose™ could not be used in a dry form for column chromatography because column chromatography employs the flow of liquid through the column.

The Examiner stated that applicant's arguments, filed October 8, 2004, have been fully considered but are not persuasive. The Examiner noted that the applicant argues a lack of motivation to combine the references and a lack of expectation of success and that the '363 patent does not teach the attachment of R38 peptides to chromatographic beads nor that the R38 peptides could be used to treat SLE.

The Examiner suggested that had the '363 patent taught the attachment of R38 peptides to chromatographic beads it would likely have comprised 102 art. The Examiner alleged that the '363 patent clearly teaches that the R38 peptide binds "pathogenic lupus antibodies" and that the peptides have "therapeutic potential" by binding lupus antibodies.

In response, applicant respectfully traverse the Examiner's for each of the reasons which follow:

1. Extracorporeal Removal Of Antibodies That Bind To A Peptide Represented By SEQ ID NO. 1 Is Neither Taught Nor Suggested By The Cited References As A Treatment For Lupus.

U.S. Patent No. 6,228,363 to Naparstek ("the '363 patent") discloses that a peptide represented by SEQ ID NO. 1 (the "R38" peptide) can be administered to a lupus patient to treat the patient. The Examiner has stated that the '363 patent "does not disclose a method of extracorporeal removal of lupus antibodies from a subject's plasma," on page 3 of the April 5, 2004 Office Action. Thus, extracorpored removal of anti-R38 antibodies is not taught or even mentioned in the '363 patent as a treatment for lapus.

Neither of the other cited references, Goubitz et al and Madaio et al., even mention an R38 peptide or its antibody, and certainly do not teach or suggest extracorporeal removal of anti-R38 antibodies as a treatment for lupus.

The Examiner appears to recognize this deficiency in the references. The only rationale provided in the Office Actions is that one "would have been motivated to employ the R38 peptide on an immunoadsorption column given the teachings of Madaio et al. that dsDNA-Ab from lupus patients also recognize laminin and the '363 patent that the R38 peptide is derived from laminin and is recognized by pathogenic lupus antibodies." Of note, however, is that

Madaio et al. do note even mention immunioadsorption columns or any reason to remove such antibodies. In fact, on page 388, left hand column, first full paragraph, Madaio et al. detract from any motivation for doing so by stating that "although the presence of anti-DNA, anti-SmRNP and other autoantibodies are useful *diagnostic markers* in patients with lupus, serum autoantibody levels frequently do not correlate with disease activity." (emphasis added) Such a statement certainly does not motivate removal of the antibodies that bind to laminin, much less removal of antibodies that bind to R38.

Additionally with respect to Madaio et al. although the R38 peptide is derived from laminin and is recognized by certain anti-R38 antibodies, the conformation and three dimensional structure of the shorter linear R-38 peptide differs significantly from that of the larger laminin molecule. Therefore, the relevance of the teachings of Madaio et al. to applicant's claimed invention are tenuous. Certainly, antibodies that bind to laminin cannot be presumed to bind the R38 peptide.

With respect to Gaubitz et al., extracorporeal removal of antibodies to treat lupus as described by Gaubitz et al. removes all immunoglobulins. Such a teaching offers no answers to the question of whether anti-R38 antibodies should be, or even could be, removed, or whether to expect a successful treatment by doing so.

Clearly, the cited references even when combined fail to teach every element of the applicant's invention. The Examiner's assertion that the missing element is somehow

motivated by Madaio et al. is contradicted by the explicit statements to the contrary by Madaio et al. Indeed, the references cannot motivate or suggest something which they do not even mention. It is well settled that "[T]o establish a *prima facie* case of obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art." M.P.E.P. §2143.03 (Rev. 2, May 2004).

Thus, in the absence of applicant's disclosure of extracorporeal removal using the R38 peptide, one of skill in the art would understand R38 to be useful for administration to lupus patients as disclosed in the '363 patent. It is only in hindsight with the benefit of applicant's disclosure that the cited references are combined. However, the references are deficient at least in so far as they do not teach or suggest or even mention extracorpored removal of R38.

Accordingly, the rejection based on Gaubitz et al., the '363 patent, and Madaio et al. should be withdrawn.

2. Binding of an Antibody on a Plate in an ELISA Test Offers No Expectation of Binding in a Column.

Applicant also points out that the binding of an antibody to a peptide on a plate in an ELISA test does not mean the same peptide will successfully bind the same antibody when the peptide is attached, for example to a Sepharose bead. This is due to 1) differences in the conformational structure of the peptide on the plate versus the peptide on the bead, and 2) different time period of contact between

the peptides on an ELISA plate versus that on a column. As the Examiner will appreciate, the interaction of antibodies with an antigen on an ELISA plate requires an incubation of the antibody on the plate for about 1 hour, whereas the interaction of the antibodies with the antigen bound to the column occur within a couple of minutes. Therefore a reaction on an ELISA plate offers no expectation that the same reaction would occur on a column.

Therefore, it would not have been obvious to one skilled in the art based on the cited references that the R38 peptide attached to the Sepharose column would still bind the same antibodies as it did on a plate. Moreover, there is no expectation, even if any binding occurred, that it could be used to remove the antibodies from the plasma of an SLE patient.

Indeed, there are very few columns which could even be considered for treating autoimmune diseases. The Corraffin® Column was developed for the treatment of cardiomyopathy. It contains a combination of synthetic peptides and acts like a mimitope for the binding of autoantibodies that attack the alpha 1 adrenergic receptor of the heart muscle. In the MG50® column used for myasthenia gravis patients, an 18 amino-acid peptide from the target antigen was synthesized and bound to cellulose particles matrix similar to our technique (see Takamori, et al, Transfusion Science, (1996), 17:445-453, attached hereto as **Exhibit B**).

The construction of an immunoadsorption column with the R-38 peptide and its use to remove SLE specific antibodies from the plasma of SLE patients was neither

taught nor suggested by any of the cited references prior to the applicant's invention. The failure of the cited references to teach the claimed combination of column support, ligand and antigen would give one skilled in the art no expectation of success in treating SLE patients.

Therefore, the cited references do not teach or suggest the appropriate columns for use in removing specific SLE antibodies. Furthermore, successful affinity absorption columns are completely unknown for the treating SLE by the removal of specific SLE antibodies.

3. The subject invention can be scaled up.

The Examiner noted applicant's remarks of unpredictable results in removing 30-60% of the pathogenic antibodies from the plasma of an SLE patient (Example 12). The Examiner alleged that a review of Example 12 shows that just a tiny 5 ml column was employed which the Examiner hardly be considered predictive of what would, or would not, be unpredictable on the scale of the claimed method. The Examiner also alleged that in the experiments of Gaubitz et al., which were conducted on a more realistic scale according to the Examiner, up to 70% of the antibodies could be removed from an SLE patient's plasma sample.

In response, applicant notes that a person skilled in the art would recognize that the column used in Example 12 of the subject application exemplifies the larger column that would be used for human treatment. The 5 ml NHS-activated Sepharose™ column used in Example 12 removed 99% of the

anti-R38 activity of the mouse monoclonal C72 and between 30%-60% of the antibodies in the human SLE patients plasma. A larger column would be expected to remove a similar fraction from a patient's plasma.

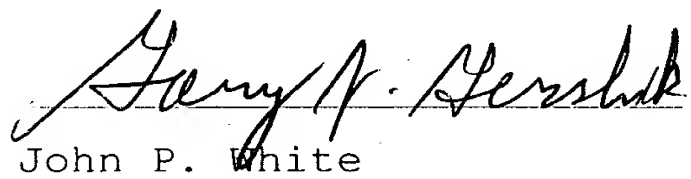
Indeed applicant has confirmed this expectation. Applicant submits a Declaration under 37 C.F.R. §1.132 (attached hereto as **Exhibit C**) which presents data showing the effectiveness of a 50 ml column. Thus, even if a *prima facie* case of obviousness was properly made, applicant's unexpected level of removal of antibodies using the R38 peptide would rebut any such case and supports a finding of patentability of the claimed invention.

Accordingly applicant maintains that claim 8-10 are not obvious over Gaubitz in view of the '363 patent and Madaio and requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 103(a).

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee other that the enclosed $1,020.00 fee for the three-month extension of time is deemed necessary in connection with the filing of this Amendment and a check in that amount is enclosed. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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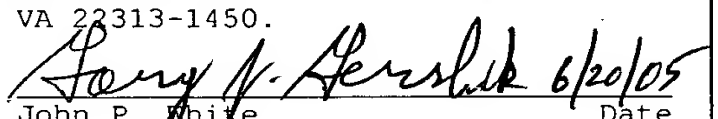
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



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